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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/580,098	02/05/2007	Adam McCluskey	65617US(54086)	5085

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EDWARDS ANGELL PALMER & DODGE LLP
P.O. BOX 55874
BOSTON, MA 02205

EXAMINER	
WEBB, WALTER E	

ART UNIT	PAPER NUMBER
1612	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/580,098	MCCLUSKEY ET AL.	
	Examiner	Art Unit	
	WALTER E. WEBB	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,26,56-58,60-66,69,70,72,73,75-79,81 and 86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 26, 56-58, 60-66, 69, 70, 72, 73, 75-79, 81 and 86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments, filed 12/1/2008, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112—previous

Written Description Rejection

Claim 86 remains rejected under 35 USC 112, first paragraph as failing to comply with the written description requirement. Claim 86, continues to recite the phrase "prodrug."

Applicant argues that the term "prodrug" was well known in the art and provides a definition in Exhibit A. However, the issue here is not whether the artisan knows what a prodrug is, but whether it was described in regard to the instant Formula I. Because there is no support for "prodrug" in the specification, it is not clear that applicant had possession of "prodrug", in general, of Formula I.

Applicant argues that the specification clearly exemplifies a range of prodrug forms and cites page 16, lines 13-27 of the specification. However, this section of the specification does not describe a prodrug species, and makes no correlation between structure and function. Nor does it describe how the groups, i.e. carbonates, carbamates, etc., are attached to the core structure.

Applicant also point to prodrug Examples, at pages 44-46, Tables 2 and 3. However, the specification does not provide a reasonably representative disclosure of useful "prodrugs" generally, a potentially huge genus inclusive of many different compounds having widely divergent structures and functions. Specifically, the specification discloses only a limited number of species and these are not viewed as being reasonably representative of the genus in its claimed scope because no readily apparent combination of identifying characteristics is provided, other than the disclosure of those specific species as examples of the claimed genus.

Enablement Rejection

Claims 1, 26, 56-58, and 60-66, 69, 70, 72, 73, 75-79, 81 and 86 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not reasonably provide enablement for prevention or treatment of disease mediated by dynamin-dependent endocytosis.

Applicant argues that the amendment to claim 1 provides enablement of the invention. However, the method of claim 1 is used in the method of treating or preventing epilepsy, as per claim 86. The amendment does not remove the enablement rejection in regard to preventing or treating epilepsy.

Applicant argues, in regard to claim 86, that the specification provides ample disclosure for one of ordinary skill in the art to practice preventing or treating epilepsy without undue experimentation. However, the disclosure provides no guidance for or examples of preventing epilepsy. While the present claims encompass preventing epilepsy, Applicant's data merely shows support for treatment through *in vitro* experimentation. Since the present specification would not enable the skilled artisan to prevent epilepsy with the claimed compound, a clear burden of undue experimentation would be placed upon the skilled artisan in order to practice the full scope of the presently claimed invention.

In regard to the scope of diseases being treated, Applicant's invention is drawn to inhibition of "a dynamin-dependent condition in a mammal." Applicant provides no guidance for treating this potentially huge genus of conditions. Epilepsy does not suffice to cover every species of this genus. The artisan would be subject to undue experimentation in determining which diseases are related to dynamin-dependent condition as well as determining which of the diseases found showed some sensitivity to a compound of formula I. Applicant's disclosure is not commensurate in scope with applicant's claims.

In regard to the scope of active agents, Applicant argues that the experiment needed to practice the invention is merely routine, although some screening might be required to identify compounds that work. Applicant has narrowed the scope of compounds claimed, and argues that a person having ordinary skill in the art can readily provide corresponding compounds in which phenyl is substituted for a heterocyclic

group. However, heterocyclic group represents a broad genus, and the term has not been limited to only phenyl. Phenyl is just an example. Claim 1 states that Z can be a heterocyclic group of one ring having 5 or 6 ring members and at least two substituents. Heterocycles are also claimed for W, V, and Y as well. Guidance is needed in regard to the predictability of this broad genus in preventing or treating dynamin-dependent conditions.

Claim Rejections - 35 USC § 103--previous

1) Claims 1 and 79 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Gazit et al., (Journal of Medicinal Chemistry 1996) in view of Ahn et al., (Journal of Biological Chemistry 1999).

Applicant argues that Gazit fails to describe methods of inhibiting GTPase activity of dynamin and that Ahn fails to remedy the deficiences of Gazit, since the cell model used in Ahn is artificial and does not necessarily reflect the biology of cells that endogenously express dynamin. However, the use of an artificial cell does not suggest that the data is unreliable in providing a link between dynamin activity and Bis-T23. Dynamin is a GTPase, and its GTPase activity is recognized in the prior art as being required for endycytosis of many GPCRs and receptor tyrosine kinases (see Ahn at pg. 1185, right column, 2nd paragraph). Ahn teaches that phosphorylation of dynamin is essential for its function in endocytosis. Gazit teaches that Bis-T23 inhibits Src kinases

that phosphorylate dynamin. Thus introduction of Bis-T23 to a cell would inhibit dynamin GTPase activity, through inhibition of Src kinases.

Applicant argues that Ahn provides no evidence that Tyr mutations to phenylalanine were not themselves inhibitory to dynamin function. However, the reference concludes that c-Src-mediated tyrosine phosphorylation of dynamin is required for receptor internalization. There is nothing in the reference to support otherwise, and applicant has not provided any evidence to contradict the findings of Ahn. The artisan would reasonably rely on the conclusions of Ahn based on the data presented. Applicant's argument is unpersuasive.

Applicant cites Tan et al. and Tomizawa et al. as references that "teach away" from SVE/dynamin mediated endocytosis as being regulated by tyrosine phosphorylation of dynamin. However, these references were not used in the rejection, nor do they discount the teachings of Ahn. There is no basis for assuming that the artisan would rely solely on the teachings of Tan et al. and Tomizawa for a teaching on dynamin mediated endocytosis. Applicant's citation of these references here are unpersuasive in regard to this rejection.

Applicant argues that the artisan would not have chosen a large dimeric tyrphostin, but a monomeric compound, since the smaller monomeric compound is likely to have greater cell permeability and thereby efficacy. However, applicant provides no evidence to support this argument, which is tantamount to mere speculation as to the type of compound the artisan would have chosen to inhibit dynamin.

Futhermore, it is noted in Gazit that dimeric tyrphostins have improved efficacy over monomeric tyrphostins. Applicant's argument is not persuasive.

2) Claims 26, 56-58, 60-66, 69, 70, 72, 73, 75-78 and 81 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Gazit et al., (Journal of Medicinal Chemistry 1996) in view of Jassar et al., (Brain Research 1997). This rejection also applies to newly amended **claim 86**.

Applicant argues that Jassar fails to examine epilepsy, dynamin or endocytosis, and that it also fails to teach or suggest a role for dynamin or endocytosis, or motivation to employ dimeric tyrphostins to inhibit GTPase activity of dynamin. However, the above claims read on a method of treating epilepsy by administering Bis-T23, a dimeric tryphostin. Jassar suggests that a monomeric tyrphostin, tyrphostin B-44, would be useful in treating epilepsy, and Gazit et al. teaches that dimeric tryphostins have improved efficacy over the monomeric tyrphostin. The artisan would have been motivated to use the dimeric tyrpostin, Bis-T23, based on this improved efficacy. The fact that applicant has recognized another advantage, i.e. inhibition of the GTPase activity of dynamin, which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Walter E. Webb whose telephone number is (571) 270-3287. The examiner can normally be reached on 8:00am-4:00pm Mon-Fri EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Walter E. Webb
/Walter E Webb/
Examiner, Art Unit 1612

/Frederick Krass/

Supervisory Patent Examiner, Art Unit 1612